Citation:

Konstantynowicz J, Nguyen TV, Kaczmarski M, Jamiolkowski J, Piotrowska-Jastrzebska J, Seeman E. Fractures during growth: potential role of a milk-free diet. *Osteoporos Int.* 2007 Dec;18(12):1601-7

PubMed ID: 17516020

Study Design:

Case-Control Study

Class:

C - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

NEUTRAL: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To examine the association between intakes of calcium below the RDI, as referred to Polish recommendations, fractures and bone mineral density in children with cow's milk allergy (CMA) and 2.5 to 14 years of a milk-free diet.

Inclusion Criteria:

- Children and adolescents aged 2-20 years with CMA
- Healthy children and adolescents without CMA
- Cases were admitted with one or more fractures involving the wrist, forearm, tibia, humerus, fibula, ankle, clavicle or femoral shaft

Exclusion Criteria:

- Fractures of fingers due to severe trauma such as road accidents

Description of Study Protocol:

Recruitment : Cases and controls were recruited from North Eastern Poland between 1999-2003. In addition, healthy children and adolescents were recruited from a local public school. The cases were recruited from the Bialystok Medical University Children's Hospital.

Design: Case-control study

Blinding used (if applicable): not applicable

Intervention (if applicable): not applicable

Statistical Analysis:

- Odd ratios of fracture and the absolute fracture risk associated with a milk free diet were derived using a conditional logistic regression with a discrete logistic model stratified by matching variables
- Those associated with fracture ($p>0.1$) were used in a multivariate model with the primary exposure variable
- Univariate analyses identified potential confounders
- Bayesian analysis was carried out to evaluate the risk of sustaining a fracture in those exposed to CMA.

Data Collection Summary:

Timing of Measurements:

- Majority of CMA were diagnosed during infancy
- All children with CMA were treated with a restrictive milk-free diet from 2.5 to 14 years
- In a subset of participants (7-17 years old), 24 hour recall of calcium intake was obtained. Weight, height, bone mineral density and body composition were measured.

Dependent Variables

- Fractures were ascertained by interview and from medical records
- Bone mineral content (BMC)
- Bone mineral density (BMD)
- Weight
- Height
- Body composition

Independent Variables

- Milk free diet was introduced during the first year/first months of life in the majority of CMA patients. The number of patients in a free milk diet diminished as children became older. Seventy-eighty per cent of the children with CMA were under 11 years.
- Calcium intake was assessed by 24 hour recall using a modified version of youth-adolescent questionnaire (YAQ) during a direct interview

Control Variables

- Age

Description of Actual Data Sample:

Initial N: 364 subjects: 91 cases and 273 controls

Attrition (final N): 364 (91 cases: 57 boys, 34 girls; 273 controls: 171 boys, 102 girls). For each fracture case, 3 controls without fracture were randomly sampled from 884 controls.

Age: 2.5 to 20 years

Ethnicity: Caucasian

Other relevant demographics:

- Of all fracture cases, 32% were in the first decade and 68% in the second decade of life.
- Forty-six participants aged 7-17 years old on a milk-free diet were assessed for calcium intake.
- All cases and controls were free of chronic diseases or prolonged use of medication known to affect bone metabolism.

Anthropometrics: No significant differences were found in age-, weight-, height and BMI adjusted BMC and BMD between CMA patients and those on normal diets.

Location: North Eastern Poland, Poland

Summary of Results:

Key Findings

- In girls, 29.4% of cases and 11.8% of controls had a history of milk-free diet producing an odds ratio for fracture associated with a milk-free diet of 4.6 (95% confidence interval: 1.4 - 15.5, $P < 0.01$).
- In boys, 23% of cases and 19% of controls had a history of a milk-free diet, odds ratio = 1.3 (95% confidence interval: 0.6 - 2.7, NS).
- If the prevalence of CMA in the population is only 5%, only 6.7% of the fractures occurring are attributable to CMA and the associated nutritional deficit.

Other Findings

- The duration of milk-free diet was longer in girls with fractures compared to those without (1.94 yr vs 0.73 yr, p=0.002) but not in boys (1.08 vs 0.9 yr, p=0.57)
- No association was found between calcium intake, BMD or fracture prevalence in a subset of children and adolescents with 7-17 years old.
- Body fat mass was not associated with fractures. However, higher lean mass and BMC was associated with lower risk of fractures in boys (OR per 15kg: 0.52; 95%CI: 0.3-1.0 ; OR per 15kg: 0.65; 95% CI:0.4-1.0; respectively) but not girls (OR per 10kg:0.56; 95% CI:0.2-1.6 and OR per 10kg: 0.62; 95%CI:0.3-1.5; respectively).
- The association between CMA, milk-free diet and fracture remained significant in girls after adjusting for these potential confounders (OR=4.26 (95% CI:1.24-14-69).
- When there was an assumption that a fracture incidence in adolescents was 1% per year and there was a 30% of prevalence in calcium deficiency in a population, and that calcium supplementation or milk reduces fracture risk by 30%, then 15% of the fractures will be prevented. With the same assumptions, a prevalence of calcium deficiency of 20%, the number of fractures prevented ranged from 6% to 13%.

Estimates of excess risk for fracture conferred by a low milk intake due to cow's milk allergy

	Background fracture incidence (% in the population)

	1%	2%	3%
Girls fracture incidence for subjects exposed to CMA	2.45	4.84	7.15
excess risk	1.45	2.84	4.15
Boys fracture incidence for subjects exposed to CMA	1.21	2.42	3.63
excess risk	0.21	0.42	0.63

Author Conclusion:

Cow's milk allergy is associated with increased fracture risk in girls. Whether this association is due to illness, calcium deficit or a deficit in other milk nutrients is uncertain. These data suggest that the contribution of milk-free diet to fracture liability among children and adolescents is modest.

Reviewer Comments:

- *The authors recognize that CMA has a low prevalence. Thus, the attributable risk for fractures in the community will be small. Therefore, the increased risk for fractures may have been due to the disease or a deficiency in milk products other than calcium.*
- *In a subset of participants (7-17 years old), 24 hour recall of calcium intake was obtained.*

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions

1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	N/A
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes

3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	N/A

Validity Questions

1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	???
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	???
2.4.	Were the subjects/patients a representative sample of the relevant population?	???
3.	**Were study groups comparable?**	Yes
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	Yes
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	Yes
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	Yes
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	N/A
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	Yes

3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	Yes
4.1.	Were follow-up methods described and the same for all groups?	Yes
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	Yes
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	N/A
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	N/A
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	Yes
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	Yes
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	N/A
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A

6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	N/A
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	???
7.1.	Were primary and secondary endpoints described and relevant to the question?	N/A
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	???
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	No
7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	???
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	???
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
8.6.	Was clinical significance as well as statistical significance reported?	Yes
8.7.	If negative findings, was a power calculation reported to address type 2 error?	N/A
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**	Yes
9.1.	Is there a discussion of findings?	Yes
9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**	???

10.1.	Were sources of funding and investigators' affiliations described?	No
10.2.	Was the study free from apparent conflict of interest?	???